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(54) **PIPERAZINE DERIVATIVE AND DRUG CONTAINING THE SAME.**

(57) A piperazine derivative represented by general formula (I) and a salt thereof, wherein B represents phenyl or pyridyl; m represents an integer of 2 or 3; p represents an integer of 1 or 2; R^1 represents hydrogen or halogen; and A represents $-COOR^2$, $-Y-(CH_2)_n-R^3$, (a), (b) or (c), wherein R^2 represents hydrogen or lower alkyl, Y represents sulfur, oxygen, NH or <-CONH- wherein <- represents a linkage with $(CH_2)_m$; n represents an integer

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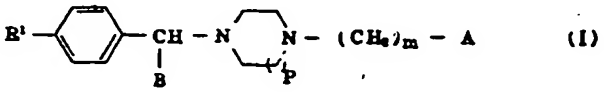
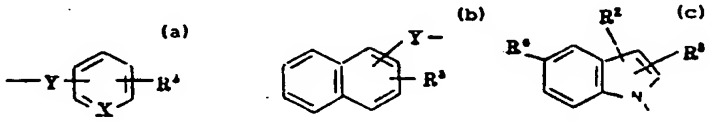
of 0 to 3; R^3 represents cyano, amino, hydroxymethyl, 1H-tetrazolyl, 1-imidazolylcarbonyl, etc.; X represents CH or nitrogen; and R^6 represents hydrogen or lower alkoxy. The compound has potent antihistaminic and antiallergic activities and high safety, and hence is excellent as antihistaminic, antiallergic and antiasthmatic drugs.



(I)



Technical Field

The present invention relates to novel piperazine derivatives and pharmaceuticals containing the same.

Background Art

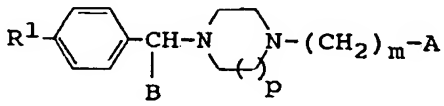
Numerous piperazine derivatives have heretofore been synthesized and studied for various pharmacological effects. Among them, those having both antiallergic and antihistamic effects are known.

For example, compounds having the diphenylmethylpiperazine skeleton are disclosed in Japanese Patent Laid-Open Nos. 32474/1981, 149282/1982, 11072/1991 and the like. These compounds, however, are accompanied by one or more drawbacks such that their pharmacological effects are still insufficient and/or they are questionable in safety.

With a view toward preparing a compound having still better antiallergic and antihistamic effects and in addition, has a high degree of safety, the present inventors have carried out an extensive investigation. As a result, they have completed the present invention.

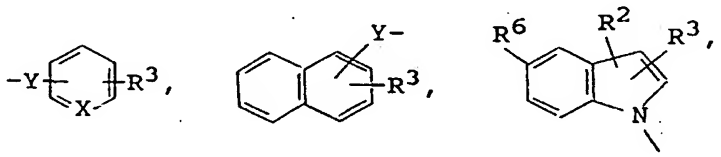
Disclosure of the Invention

The present invention relates a piperazine derivative represented by the following formula (I):

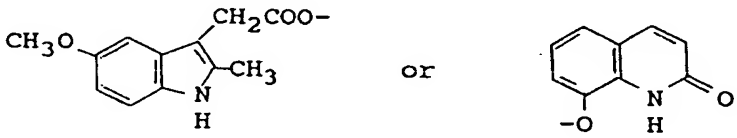


(I)

wherein B represents a phenyl or pyridinyl group, m stands for an integer of 2 or 3, p stands for an integer of 1 or 2, R^1 represents a hydrogen or halogen atom, A represents $-COOR^2$, $-Y-(CH_2)n-R^3$,



in which R^2 represents a hydrogen atom or a lower alkyl group, Y represents a sulfur or oxygen atom, NH or ←CONH- (← indicates a bond with a $(CH_2)_m$ group), n stands for an integer of 0 to 3, R^3 represents a cyano, amino, hydroxymethyl, 1H-tetrazole, 1-imidazolylcarbonyl, $-CO-COOR^4$, $-(CH_2)_\ell-COOR^4$ or $-(CH_2)_\ell-CONH-R^5$ group (R^4: hydrogen atom or lower alkyl group, ℓ: integer of 0 to 3; and R^5: 1H-tetrazole, thiazol-2-yl, thiazolin-2-yl, triazol-5-yl, trimethoxyphenyl or 3,5-dimethyl-4-hydroxyphenyl group), X represents CH or a nitrogen atom and R^6 represents a hydrogen atom or a lower alkoxyl group,



with the proviso that either case where R^1, B, p, m and A represent a hydrogen atom, a phenyl group, 1, 2 and $-NH-C_6H_4-COOR^4$, respectively, or where R^1, B, p, m and A represent a chlorine atom, a phenyl group, 1, 2 and $-O-CH_2COOH$, respectively is excluded; or a salt thereof.

In addition, the present invention also relates to an antihistamic agent and an antiallergic agent each containing the piperazine derivative (I) as an active ingredient.

In the formula (I), examples of the lower alkyl group represented by R^2 or R^4 include C_{1-4} linear or branched alkyl groups, those of the lower alkoxyl group represented by R^6 include C_{1-4} linear or branched alkyl groups, and those of the halogen atom represented by R^1 include chlorine, bromine, fluorine and iodine atoms.

The piperazine derivative (I) according to the present invention can be converted to a pharmacologically-acceptable salt thereof, for example, an acid-addition salt such as the hydrochloride, nitrate, sulfate, maleate, fumarate, oxalate, citrate, hydrobromate, succinate, sulfaminate, mandelate, malonate and phosphate or a base salt such as the sodium salt, potassium salt, lithium salt or calcium salt.

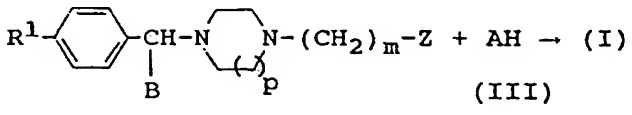
The compounds (I) according to the present invention may have stereoisomers such as optical isomers because they may contain an asymmetric carbon atom. It is to be noted that these isomers are all embraced by the present invention.

The compounds (I) according to the present invention have excellent antihistamic and antiallergic effects and also a high degree of safety as will be described later, so that they are effective as therapeutic agents for various allergic diseases, for example, as anti-inflammatory agents, therapeutics for nephritis, hepatitis or pancreatitis, preventives and/or therapeutics for respiratory diseases, and antiasthmatic drugs.

Best Modes for Carrying Out the Invention

The compound (I) of this invention can be prepared, for example, in accordance with the following process:

Process A:



(II) (III)

wherein R^1, B, p, m and A have the same meanings as defined above and Z is a halogen atom.

In other words, the compound (I) according to the present invention can be prepared by reacting a piperazine derivative represented by the formula (II) with a compound represented by the formula (III) in the presence of a base.

It is preferred to conduct the above reaction in a solvent which does not affect the reaction. Examples of the solvent include water; esters such as methyl acetate and ethyl acetate; ethers such as diethyl ether, diisopropyl ether, tetrahydrofuran and dioxane; ketones such as acetone and methyl ethyl ketone; halogenated hydrocarbons such as dichloromethane and chloroform; aromatic hydrocarbons such as benzene, toluene and xylene; acetonitrile; dimethylsulfoxide; and dimethylformamide. They may be used either singly or in combination. The reaction temperature may be varied depending on the starting compounds employed. In general, it is advantageous to select a temperature within a range of from 0 °C to a reflux temperature under normal pressure.

Examples of the base include carbonates such as potassium carbonate, sodium carbonate, sodium hydrogencarbonate and potassium hydrogencarbonate; alkali metal hydroxides such as potassium hydroxide, sodium hydroxide and lithium hydroxide; and organic bases such as triethylamine, diisopropylamine, DBU (1,8-diaza-bicyclo[5.4.0]-7-undecene).

When the compound represented by the formula (III) is a carboxylic acid ester, the corresponding carboxylic acid can be obtained by subjecting the invention compound (I), which has been prepared by the above reaction, to hydrolysis in a manner known *per se* in the art. The resulting carboxylic acid is then condensed with carbodiimidazole, 5-amino-1H-tetrazole, 2-aminothiazole, 2-aminothiazolidine, 5-aminotriazole, 3,4,5-trimethoxyaniline or 3,5-dimethyl-4-hydroxy-aniline, leading to the preparation of another invention compound.

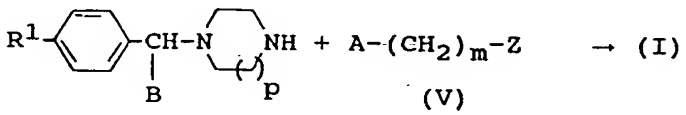
It is desirable to conduct the above condensation, in a manner known to date, in a solvent which does not affect the reaction. Examples of the solvent include esters such as methyl acetate and ethyl acetate; amides such as dimethylformamide and diethylformamide; ethers such as diethyl ether, diisopropyl ether, tetrahydrofuran and dioxane; halogenated hydrocarbons such as dichloromethane and chloroform; aromatic

hydrocarbons such as benzene, toluene and xylene; acetonitrile; and dimethylsulfoxide. These solvents can be used either singly or in combination. The reaction temperature may be varied depending on the starting compounds employed. In general, it is advantageous to select a temperature within a range of from 0 °C to a reflux temperature under normal pressure.

When the compound represented by the formula (III) is a cyano-containing compound, the invention compound (I) prepared by the above reaction can be converted to another invention compound containing a 1H-tetrazole group by reacting the invention compound (I) with tri-n-butyltin azide in the presence of a base. It is desirable to conduct the reaction in a solvent which does not affect the reaction. Examples of the solvent include esters such as methyl acetate and ethyl acetate; ethers such as diethyl ether, diisopropyl ether, tetrahydrofuran and dioxane; halogenated hydrocarbons such as dichloromethane and chloroform; aromatic hydrocarbons such as benzene, toluene and xylene; and dimethylformamide. These solvents can be used either singly or in combination. The reaction temperature may be varied depending on the starting compounds employed. In general, it is advantageous to select a temperature within a range of from room temperature to a reflux temperature under normal pressure. As the base, those similar to the bases exemplified above can be employed.

Process B:

The invention compound can also be prepared by the following process:



(IV) (V) (I)

wherein Z, R^1, B, p, m and A have the same meanings as defined above.

In other words, the compound (I) according to the present invention can be prepared by subjecting a compound represented by the formula (IV) and a compound represented by the formula (V) to condensation in the presence of a base.

It is preferred to conduct the above reaction in a solvent which does not affect the reaction. Examples of the solvent include esters such as methyl acetate and ethyl acetate; ethers such as diethyl ether, diisopropyl ether, tetrahydrofuran and dioxane; ketones such as acetone and methyl ethyl ketone; halogenated hydrocarbons such as dichloromethane and chloroform; aromatic hydrocarbons such as benzene, toluene and xylene; acetonitrile; dimethylsulfoxide; and dimethylformamide. They can be used either singly or in combination. The reaction temperature may be varied depending on the starting compounds employed. In general, it is advantageous to select a temperature within a range of from 0 °C to a reflux temperature under normal pressure. As the base, bases similar to those exemplified in the Process A are usable.

When the compound represented by the formula (V) is a carboxylic acid ester or a cyano-containing compound, the invention compound so obtained can be converted to a corresponding invention compound of another type by treating it in a similar manner to Process A.

When the starting compound (II) or (IV) has an asymmetric carbon atom in Process A or Process B, the invention compound (I) so obtained includes corresponding stereoisomers.

Among the invention compounds (I) obtained as described above, the followings are representatives ones except for the compounds to be described in Examples.

- 2-[3-[4-[(4-Chlorophenyl)phenylmethyl]-1-piperazinyl]propoxy]-N-3,4,5-trimethoxyphenyl-benzamide
- 2-[3-[4-[(4-Chlorophenyl)phenylmethyl]-1-piperazinyl]propoxy]-N-(3,5-dimethyl-4-hydroxy-phenyl)-benzamide
- 3-[3-[4-[(4-Chlorophenyl)phenylmethyl]-1-piperazinyl]propoxy]benzoic acid
- 3-[3-[4-[(4-Chlorophenyl)phenylmethyl]-1-piperazinyl]propoxy]-N-1H-tetrazol-5-yl-benzamide
- 2-[[3-[4-[(4-Chlorophenyl)phenylmethyl]-1-piperazinyl]propyl]thio]benzoic acid
- 2-[[3-[4-[(4-Chlorophenyl)phenylmethyl]-1-piperazinyl]propyl]thio]-N-1H-tetrazol-5-yl-benzamide
- 2-[3-[4-[(4-Chlorophenyl)phenylmethyl]-1-piperazinyl]propoxy]nicotinic acid
- 2-[3-[4-[(4-Chlorophenyl)phenylmethyl]-1-piperazinyl]propoxy]-N-1H-tetrazol-5-yl-nicotinamide
- 3-[2-[4-[(4-Chlorophenyl)phenylmethyl]-1-homopiperazinyl]ethoxy]benzoic acid

- 3-[2-[4-[(4-Chlorophenyl)phenylmethyl]-1-homopiperazinyl]ethyl]-N-1H-tetrazol-5-yl-benzamide
- Ethyl 4-[[2-[4-[(4-chlorophenyl)phenylmethyl]-1-homopiperazinyl]ethyl]thio]benzoate
- 4-[[2-[4-[(4-Chlorophenyl)phenylmethyl]-1-homopiperazinyl]ethyl]thio]-N-1H-tetrazol-5-yl-benzamide
- 3-[2-[4-[(4-Chlorophenyl)phenylmethyl]-1-homopiperazinyl]ethoxy]phenylacetic acid
- 3-[2-[4-[(4-Chlorophenyl)phenylmethyl]-1-homopiperazinyl]ethoxy]-N-1H-tetrazol-5-yl-phenylacetamide
- 4-[2-[4-[(4-Chlorophenyl)phenylmethyl]-1-homopiperazinyl]ethoxy]-N-1H-tetrazol-5-yl-anthranylamide
- Propyl 2-[2-[4-[(4-chlorophenyl)phenylmethyl]-1-homopiperazinyl]ethoxy]nicotinate
- 2-[2-[4-[(4-Chlorophenyl)phenylmethyl]-1-homopiperazinyl]ethoxy]-N-1H-tetrazol-5-yl-nicotinamide
- 2-[[2-[4-[(4-Chlorophenyl)phenylmethyl]-1-homopiperazinyl]ethyl]thio]acetic acid
- 1-[2-[4-[(4-Chlorophenyl)phenylmethyl]-1-homopiperazinyl]ethyl]-3-indolecarboxylic acid
- 1-[2-[4-[(4-Chlorophenyl)phenylmethyl]-1-homopiperazinyl]ethyl]-N-1H-tetrazol-5-yl-3-indoleamide
- Butyl 4-[3-[4-[(4-chlorophenyl)phenylmethyl]-1-homopiperazinyl]propoxy]benzoate
- 4-[3-[4-[(4-Chlorophenyl)phenylmethyl]-1-homopiperazinyl]propoxy]-N-1H-tetrazol-5-yl-benzamide
- Methyl 2-[3-[4-[(4-chlorophenyl)phenylmethyl]-1-homopiperazinyl]propoxy]naphthoate
- 2-[3-[4-[(4-Chlorophenyl)phenylmethyl]-1-homopiperazinyl]propoxy]naphthoic acid
- 4-[3-[4-[(4-Chlorophenyl)phenylmethyl]-1-homopiperazinyl]propoxy]-N-1H-tetrazol-5-yl-naphthamide
- 2-[2-[4-(Diphenylmethyl)-1-piperazinyl]ethoxy]-N-1H-triazol-5-yl-benzamide
- 2-[2-[4-(Diphenylmethyl)-1-piperazinyl]ethyl]thio]-N-1H-tetrazol-5-yl-benzamide
- 2-[2-[4-(Diphenylmethyl)-1-piperazinyl]ethoxy]-N-1H-tetrazol-5-yl-nicotinamide
- 1-[2-[4-(Diphenylmethyl)-1-piperazinyl]ethyl]-N-1H-tetrazol-5-yl-2-indoleamide
- 4-[2-[4-(Diphenylmethyl)-1-piperazinyl]ethoxy]-[N-1H-tetrazol-5-yl]-benzene
- 4-[2-[4-(Diphenylmethyl)-1-piperazinyl]ethoxy]benzamide
- 4-[3-[4-(Diphenylmethyl)-1-piperazinyl]propoxy]-N-3,4,5-trimethoxyphenyl-benzamide
- 4-[3-[4-(Diphenylmethyl)-1-piperazinyl]propoxy]thiazol-2-yl-benzamide
- 4-[3-[4-(Diphenylmethyl)-1-piperazinyl]propyl]thio]benzoic acid
- 4-[3-[4-(Diphenylmethyl)-1-piperazinyl]propyl]thio]-N-1H-tetrazol-5-yl-benzamide
- 2-[3-[4-(Diphenylmethyl)-1-piperazinyl]propoxy]anthranilic acid
- 2-[3-[4-(Diphenylmethyl)-1-piperazinyl]propoxy]-N-1H-tetrazol-5-yl-anthranilamide
- 2-[3-[4-(Diphenylmethyl)-1-piperazinyl]propoxy]nicotinic acid
- 2-[3-[4-(Diphenylmethyl)-1-piperazinyl]propoxy]-N-1H-tetrazol-5-yl-nicotinamide
- 1-[3-[4-(Diphenylmethyl)-1-piperazinyl]propyl]-2-indolecarboxylic acid
- 1-[3-[4-(Diphenylmethyl)-1-piperazinyl]propyl]-2-N-1H-tetrazol-5-yl-indoleamide
- 4-[3-[4-(Diphenylmethyl)-1-piperazinyl]propoxy]benzonitrile
- Butyl 2-[[3-[4-(diphenylmethyl)-1-piperazinyl]propyl]thio]acetate
- 2-[[3-14-(Diphenylmethyl)-1-piperazinyl]propyl]thio]acetic acid
- 2-[3-[4-(Diphenylmethyl)-1-piperazinyl]propoxy]-N-1H-tetrazol-5-yl-acetamide
- 1-[3-[4-(Diphenylmethyl)-1-piperazinyl]propoxy]naphthoic acid
- 1-[3-[4-(Diphenylmethyl)-1-piperazinyl]propoxy]-N-1H-tetrazol-5-yl-naphthoamide
- Ethyl 2-[3-[4-(diphenylmethyl)-1-homopiperazinyl]propoxy]benzoate
- 2-[3-[4-(Diphenylmethyl)-1-homopiperazinyl]propoxy]-N-1H-tetrazol-5-yl-benzamide
- Methyl 2-[3-[4-(diphenylmethyl)-1-homopiperazinyl]propoxy]naphthoate
- 2-[3-[4-(Diphenylmethyl)-1-homopiperazinyl]propoxy]naphthoic acid
- 2-[3-[4-(Diphenylmethyl)-1-homopiperazinyl]propoxy]-N-1H-tetrazol-5-yl-naphthoamide
- Propyl 3-[2-[4-[2-(4-chlorophenyl)pyridylmethyl]-1-piperazinyl]ethoxy]benzoate
- 3-[2-[4-[2-(4-Chlorophenyl)pyridylmethyl]-1-piperazinyl]ethoxy]-N-1H-tetrazol-5-yl-benzamide
- 2-[[2-[4-[2-(4-Chlorophenyl)pyridylmethyl]-1-piperazinyl]ethyl]thio]benzoic acid
- 2-[[2-[4-[2-(4-Chlorophenyl)pyridylmethyl]-1-piperazinyl]ethyl]thio]-N-1H-tetrazol-5-yl-benzamide
- 2-[2-[4-[2-(4-Chlorophenyl)pyridylmethyl]-1-piperazinyl]ethoxy]anthranilic acid
- 2-[2-[4-[2-(4-Chlorophenyl)pyridylmethyl]-1-piperazinyl]ethoxy]-N-1H-tetrazol-5-yl-anthranilamide
- 1-[2-[4-[2-(4-Chlorophenyl)pyridylmethyl]-1-piperazinyl]ethyl]-3-ethoxycarbonyl-indole
- 1-[2-[4-[2-(4-Chlorophenyl)pyridylmethyl]-1-piperazinyl]ethyl]-N-1H-tetrazol-5-yl-3-indoleamide
- 3-[2-[4-[2-(4-Chlorophenyl)pyridylmethyl]-1-piperazinyl]ethoxy]benzonitrile
- 4-[2-[4-[2-(4-Chlorophenyl)pyridylmethyl]-1-piperazinyl]ethoxy]benzoylimidazole
- 2-[2-[4-[2-(4-Chlorophenyl)pyridylmethyl]-1-piperazinyl]ethoxy]-N-1H-tetrazol-5-yl-acetamide
- 2-[2-[4-[2-(4-Chlorophenyl)pyridylmethyl]-1-piperazinyl]ethoxy]-1H-tetrazole-5-ylmethyl
- 4-[3-[4-[2-(4-Chlorophenyl)pyridylmethyl]-1-piperazinyl]propoxy]benzoic acid
- 4-[3-[4-[2-(4-Chlorophenyl)pyridylmethyl]-1-piperazinyl]propyl]-N-1H-tetrazol-5-yl-benzamide
- Butyl 3-[2-[4-[2-(4-chlorophenyl)pyridylmethyl]-1-homopiperazinyl]ethoxy]benzoate

- 3-[2-[4-[2-(4-Chlorophenyl)pyridylmethyl]-1-homopiperazinyl]ethoxy]-N-1H-tetrazol-5-yl-benzamide
- Ethyl 1-[2-[4-[2-(4-chlorophenyl)pyridylmethyl]-1-homopiperazinyl]ethoxy]naphthoate
- 1-[2-[4-[2-(4-Chlorophenyl)pyridylmethyl]-1-homopiperazinyl]ethoxy]naphthoic acid
- 1-[2-[4-[2-(4-Chlorophenyl)pyridylmethyl]-1-homopiperazinyl]ethoxy]-N-1H-tetrazol-5-yl-naphthoamide
- 2-[3-[4-[2-(4-Chlorophenyl)pyridylmethyl]-1-homopiperazinyl]propoxy]benzoic acid
- 2-[3-[4-[2-(4-Chlorophenyl)pyridylmethyl]-1-homopiperazinyl]propoxy]-N-1H-tetrazol-5-yl-benzamide
- 2-[3-[4-[2-(4-Chlorophenyl)pyridylmethyl]-1-homopiperazinyl]propoxy]naphthoic acid
- 2-[3-[4-[2-(4-Chlorophenyl)pyridylmethyl]-1-homopiperazinyl]propoxy]-N-1H-tetrazol-5-yl-naphthoamide
- 2-[[2-[4-(2-Phenyl-pyridylmethyl)-1-piperazinyl]ethyl]thio]benzoic acid
- 2-[[2-[4-(2-Phenyl-pyridylmethyl]-1-piperazinyl]ethyl]thio]-N-1H-tetrazol-5-yl-benzamide
- 2-[2-[4-(2-Phenyl-pyridylmethyl)-1-piperazinyl]ethoxy]anthranilic acid
- 2-[2-[4-(2-Phenyl-pyridylmethyl)-1-piperazinyl]ethoxy]-N-1H-tetrazol-5-yl-anthranilamide
- 2-[2-[4-(2-Phenyl-pyridylmethyl)-1-piperazinyl]ethoxy]nicotinic acid
- 2-[2-[4-(2-Phenyl-pyridylmethyl)-1-piperazinyl]ethyl]-N-1H-tetrazol-5-yl-nicotinamide
- Methyl 2-[3-[4-(2-phenyl-pyridylmethyl)-1-piperazinyl]propoxy]benzoate
- 2-[3-[4-(2-phenyl-pyridylmethyl)-1-piperazinyl]propoxy]-N-1H-tetrazol-5-yl-benzamide
- Propyl 2-[3-[4-(2-phenyl-pyridylmethyl)-1-piperazinyl]propoxy]naphthoate
- 2-[3-[4-(2-Phenyl-pyridylmethyl)-1-piperazinyl]propoxy]naphthoic acid
- 2-[3-[4-(2-Phenyl-pyridylmethyl)-1-piperazinyl]propoxy]-N-1H-tetrazol-5-yl-naphthoamide
- 3-[2-[4-(2-Phenyl-pyridylmethyl)-1-homopiperazinyl]ethoxy]benzoic acid
- 3-[2-[4-(2-Phenyl-pyridylmethyl)-1-homopiperazinyl]ethoxy]-N-1H-tetrazol-5-yl-benzamide
- Methyl 1-[2-[4-(2-phenyl-pyridylmethyl)-1-homopiperazinyl]ethoxy]naphthoate
- 1-[2-[4-(2-Phenyl-pyridylmethyl)-1-homopiperazinyl]ethoxy]naphthoicacid
- 1-[2-[4-(2-Phenyl-pyridylmethyl)-1-homopiperazinyl]ethoxy]-N-1H-tetrazol-5-yl-naphthoamide
- Ethyl 2-[3-[4-(2-phenyl-pyridylmethyl)-1-homopiperazinyl]propoxy]benzoate
- 2-[3-[4-(2-Phenyl-pyridylmethyl)-1-homopiperazinyl]propoxy]-N-1H-tetrazol-5-yl-benzamide
- Ethyl 2-[3-[4-(2-phenyl-pyridylmethyl)-1-homopiperazinyl]propoxy]naphthoate
- 2-[3-[4-(2-Phenyl-pyridylmethyl)-1-homopiperazinyl]propoxy]naphthoic acid
- 2-[3-[4-(2-Phenyl-pyridylmethyl)-1-homopiperazinyl]propoxy]-N-1H-tetrazol-5-yl-naphthoamide

The compound (I) according to the present invention can be formulated into dosage forms suited for oral administration or parenteral administration by adding one or more pharmaceutically-acceptable auxiliary agents thereto.

Solid dosage forms for oral administration include tablets, powders, granules and capsules. The invention compound (I) can be formulated into such a solid preparation by combining it with one or more suitable additives such as excipients, e.g., lactose, mannitol, corn starch or crystalline celluiose; binders, e.g., a cellulose derivative, gum arabic or gelatin; disintegrators, e.g., calcium carboxymethylcellulose; and lubricants such as talc and magnesium stearate. The solid preparation so obtained can be converted into an enteric coated one by coating it with a coating base material such as hydroxypropylmethylcellulose phthalate, hydroxypropylmethylcellulose acetate succinate, cellulose acetate phthalate or a methacrylate copolymer.

Exemplary liquid preparations for oral administration include emulsions, solutions, suspensions, syrups and elixirs. The compound (I) according to the present invention can be prepared into the form of a liquid preparation by combining an inert diluent such as purified water or ethanol. In addition to the inert diluent, auxiliary agents such as a humectant and a suspending agent, a sweetener, a taste improver, an aromatic agent and/or an antiseptic can be added. The compound can also be used in the form of an aerosol preparation which is formulated in a manner known *per se* in the art.

Examples of the liquid preparation for parenteral administration include injections. The invention compound (I) can be formulated into the form of an injection by combining the compound with water, ethanol, glycerin and a conventional surfactant. Further, the compound can also be used in the form of a surface application drug such as an inhalation, liquid for external use, ophthalmic solution, nasal drops or ointment.

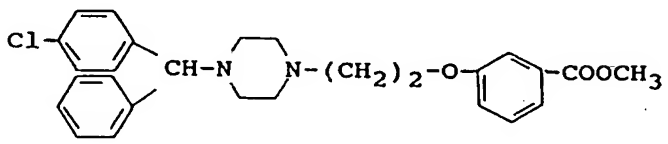
The dosage of the compound (I) of the present invention varies depending on the age, weight, conditions, therapeutic effects, administration method, administration period, etc. In general, it is desirable to orally administer the compound (I) at a daily dosage of 1-500 mg/day, particularly 5-50 mg/day, in 1-3 portions a day or to parenterally administer it at a dosage of 0.1-500 mg/day in one to several portions a day.

Examples

The present invention will hereinafter be described more specifically by the following examples. It is, however, to be borne in mind that the present invention is by no means limited to or by them. In each table, Ph and Py indicate a phenyl group and a 2-pyridinyl group, respectively.

Example 1

Methyl 3-[2-[4-[(4-chlorophenyl)phenylmethyl]-1-piperazinyl]ethoxy]benzoate



In acetone, 16.0 g (38 mmol) of 2-[4-[(4-chlorophenyl)phenylmethyl]-1-piperazinyl]ethyl chloride·dihydrochloride and 18.3 g of potassium carbonate were suspended, followed by the addition of 6.9 g (45 mmol) of methyl 3-hydroxybenzoate. The resulting suspension was refluxed at 70 °C for 24 hours. After the reaction mixture was allowed to cool down, 200 mℓ of water were added, followed by extraction with 200 mℓ portions of ethyl acetate twice. The ethyl acetate layers were washed with water and dried over anhydrous magnesium sulfate. The solvent was thereafter distilled off. The residue so obtained was purified by chromatography on a silica gel column (ethyl acetate:n-hexane = 1:1), whereby 12 g of the title compound were obtained. Yield: 68%.

Melting point (decomposition point): 200-205 °C (dihydrochloride)

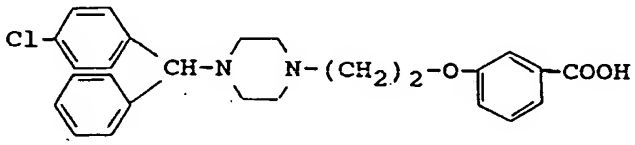
MS (m/z): 464(M^+)

IR (nujol) cm^{-1}: 3400, 2350, 1710

NMR (DMSO-d_6) δ: (oxalate) 2.55(4H,brs), 3.23(4H,brs), 3.40(2H,t), 3.85(3H,s), 4.35(2H,t), 4.47(1H,s), 7.22-7.59(13H,m)

Example 2

3-[2-[4-[(4-Chlorophenyl)phenylmethyl]-1-piperazinyl]ethoxy]benzoic acid



In 200 mℓ of ethanol, 10 g of the methyl 3-[2-[4-[(4-chlorophenyl)phenylmethyl]-1-piperazinyl]ethoxy]-benzoate obtained in Example 1 and 50 mℓ of 10% sodium hydroxide were dissolved, followed by stirring at 50 °C for one hour. After the reaction mixture was allowed to cool down, the solvent was distilled off under reduced pressure. Water (200 mℓ) was added to the residue, followed by the addition of acetic acid to adjust its pH to 4.0. The resulting mixture was extracted with 200 mℓ portions of ethyl acetate twice. The ethyl acetate layers so obtained were washed with water and then dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure. The residue so obtained was purified by chromatography on a silica gel column (chloroform:methanol = 10:1), whereby 6.6 g of the title compound were obtained. Yield: 69%.

Melting point (decomposition point): 202-203 °C

MS (m/z): 450(M^+)

IR (nujol) cm^{-1}: 3400, 1705, 1580

NMR (DMSO-d_6) δ: 2.77(1H,brs), 3.35-3.42(8H,m), 3.50(2H,t), 4.46(2H,t), 4.51(1H,s), 7.22-7.58(13H,m)

Examples 3-39

The compounds of Examples 3-39 shown in Tables 1-8 were each obtained in accordance with the procedures of Example 1 or Example 2. The names of the respective compounds will be described below.

Example 3

Methyl 2-[2-[4-[(4-chlorophenyl)phenylmethyl]-1-piperazinyl]ethoxy]benzoate

Examples 4 & 5

2-[2-[4-[(4-Chlorophenyl)phenylmethyl]-1-piperazinyl]ethoxy]benzoic acid

Example 6

Methyl 4-[2-[4-[(4-chlorophenyl)phenylmethyl]-1-piperazinyl]ethoxy]benzoate

Example 7

4-[2-[4-[(4-Chlorophenyl)phenylmethyl]-1-piperazinyl]ethoxy]benzoic acid

Example 8

Methyl 2-[2-[4-(diphenylmethyl)-1-piperazinyl]ethoxy]benzoate

Example 9

2-[2-[4-(Diphenylmethyl]-1-piperazinyl]ethoxy]benzoic acid

Example 10

Methyl 2-[3-[4-[(4-chlorophenyl)phenylmethyl]-1-piperazinyl]propoxy]benzoate

Example 11

2-[3-[4-[(4-Chlorophenyl)phenylmethyl]-1-piperazinyl]propoxy]benzoic acid

Example 12

2-[2-[4-[(4-Chlorophenyl)phenylmethyl]-1-piperazinyl]ethoxy]benzyl alcohol

Example 13

2-[2-[4-[(4-Chlorophenyl)phenylmethyl]-1-piperazinyl]ethoxy]benzonitrile

Example 14

3-[2-[4-[(4-Chlorophenyl)phenylmethyl]-1-piperazinyl]ethoxy]benzonitrile

Example 15

[3-[4-(Diphenylmethyl]-1-piperazinyl]N-propionyl]anthranilic acid

Example 16

Methyl 1-[2-[4-[(4-chlorophenyl)phenylmethyl]-1-piperazinyl]ethoxy]naphthoate

Example 17

1-[2-[4-[(4-Chlorophenyl)phenylmethyl]-1-piperazinyl]ethoxy]naphthoic acid

Example 18

Methyl 2-[2-[4-[(4-chlorophenyl)phenylmethyl]-1-piperazinyl]ethoxy]naphthoate

Example 19

2-[2-[4-[(4-Chlorophenyl)phenylmethyl]-1-piperazinyl]ethoxy]naphthoic acid

Example 20

3-[1-[2-[4-[(4-Chlorophenyl)phenylmethyl]-1-piperazinyl]ethoxycarbonylmethyl]-2-methyl-5-methoxy-indole

Example 21

1-[2-[4-[(4-Chlorophenyl)phenylmethyl]-1-piperazinyl]ethyl]-2-methyloxycarbonyl-indole

Example 22

1-[2-[4-[(4-Chlorophenyl)phenylmethyl]-1-piperazinyl]ethyl]-3-indolecarboxylic acid

Example 23

Methyl 1-[2-[4-[(4-chlorophenyl)phenylmethyl]-1-piperazinyl]ethyl]-2-methyl-5-methoxy-3-indoleacetate

Example 24

1-[2-[4-[(4-Chlorophenyl)phenylmethyl]-1-piperazinyl]ethyl]-2-methyl-5-methoxy-3-indoleacetic acid

Example 25

1-[2-[4-[(4-Chlorophenyl)phenylmethyl]-1-piperazinyl]ethyl]-2-indolecarboxylic acid

Example 26

2-[2-[4-[(4-Chlorophenyl)phenylmethyl]-1-piperazinyl]ethoxy]phenylacetic acid

Example 27

Methyl 2-[2-[4-[(4-chlorophenyl)phenylmethyl]-1-piperazinyl]ethoxy]phenylacetate

Example 28

Methyl 2-[2-[4-[(4-chlorophenyl)phenylmethyl]-1-piperazinyl]ethoxy]nicotinate

Example 29

2-[2-[4-[(4-Chlorophenyl)phenylmethyl]-1-piperazinyl]ethoxy]nicotinic acid

Example 30

8-[2-[4-(Diphenylmethyl)-1-piperazinyl]ethoxy]quinolin-N-(1H)-2-one

Example 31

2-[2-[4-[2-(4-Chlorophenyl)pyridylmethyl]-1-piperazinyl]ethoxy]benzoic acid

Example 32

Methyl 2-[2-[4-[(4-chlorophenyl)phenylmethyl]-1-homopiperazinyl]ethoxy]benzoate

Example 33

2-[2-[4-[(4-Chlorophenyl)phenylmethyl]-1-homopiperazinyl]ethoxy]benzoic acid

Example 34

Methyl 2-[2-[4-(2-phenyl-pyridylmethyl)-1-piperazinyl]ethoxy]benzoate

Example 35

2-[2-[4-(2-Phenyl-pyridylmethyl)-1-piperazinyl]ethoxy]benzoic acid

Example 36

Ethyl 4-[4-[(4-chlorophenyl)phenylmethyl]-1-piperazinyl]butyrate

Example 37

4-[4-[(4-chlorophenyl)phenylmethyl]-1-piperazinyl]butyric acid

Example 38

Methyl 2-[2-[4-(diphenyl)-1-homopiperazinyl]ethoxy]benzoate

Example 39

2-[2-[4-(Diphenyl)-1-homopiperazinyl]ethoxy]benzoic acid

Table 1

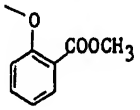
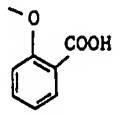
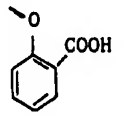
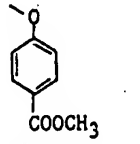
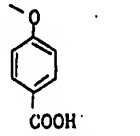
Ex.	R^1	B	m	p	A	Melting point(°C)	MS(M^+)	IR(cm^{-1}), NMR(ppm)
3	Cl	Ph	2	1		Decomposition point 210-214 (Dihydrochloride)	464	IR(nujol):1720 NMR($CDCl_3$):(2HCl)3.56(4H,brs), 3.83(3H,s),4.04(2H,t), 4.40(4H,brs),4.63(2H,t), 5.00(1H,s),6.95-7.88(13H,m)
4	Cl	Ph	2	1		Decomposition point 216-218 (Dihydrochloride)	450	IR(nujol):1690 NMR($CDCl_3$):2.34(4H,brs), 2.70(2H,t),2.97(4H,brs), 3.94(1H,s),4.03(2H,brs), 6.78-7.81(13H,m)
5	Cl	Ph	2	1		193-195 (1/2 Fumarate)	450	IR(nujol):1690 NMR(DMSO-d_6):2.36(4H,brs), 2.70(4H,brs),2.82(2H,t),4.25 (2H,t),4.33(1H,s),6.62(1H,s), 6.98-7.61(13H,m),8.25(2H,brs)
6	Cl	Ph	2	1		Decomposition point 197-199 (Dihydrochloride)	464	IR(nujol):3400,1720 NMR(DMSO-d_6):(oxalate) 2.54(4H,brs),3.22(4H,brs), 3.40(2H,t),4.37(2H,t),4.47 (1H,s),7.05-7.93(13H,m)
7	Cl	Ph	2	1		Decomposition point 230-232 (Dihydrochloride)	450	IR(nujol):3400,1700 NMR(DMSO-d_6):2.77(1H,brs), 3.34(8H,brs),3.50(2H,brs), 4.51(3H,brs),7.05-7.92(13H,m)

Table 2

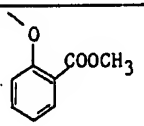
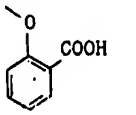
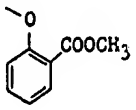
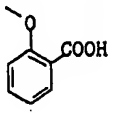
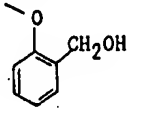
Ex.	R^1	B	m	p	A	Melting point(°C)	MS(M^+)	IR(cm^{-1}), NMR(ppm)
8	H	Ph	2	1		Decomposition point 211-213 (Dihydrochloride)	430	IR(nujol):3380,1720 NMR($CDCl_3$):(2HCl)3.58(4H,brs), 3.83(3H,s),4.01(4H,brs), 4.48(2H,t),4.61(2H,t), 5.02(1H,s),6.95-7.91(14H,m)
9	H	Ph	2	1		178-179 (Maleate)	416	IR(nujol):1675 NMR(DMSO-d_6):2.51(4H,brs), 3.38(4H,brs),3.46(2H,t), 4.37(2H,t),4.46(1H,s), 7.04-7.70(14H,m)
10	Cl	Ph	3	1		114-117 (Maleate)	478	NMR(DMSO-d_6):2.15(2H,m), 2.30(2H,m),2.83(2H,brs),3.15 (2H,brs),3.31(2H,t),3.50(2H,m), 3.78(3H,s),4.13(2H,t),4.56(1H, s),6.14(4H,s),7.05-7.73(13H,m)
11	Cl	Ph	3	1		- (powder)	464	IR(nujol):3420,1680 NMR(DMSO-d_6):(2HCl)2.21(2H,t), 3.15(4H,brs),3.35(4H,brs), 3.57(1H,s),3.60(2H,m),4.14 (2H,t),7.03-7.72(14H,m)
12	Cl	Ph	2	1		- (powder)	436	IR(nujol):3350 NMR($CDCl_3$):2.42(4H,brs),2.54 (4H,brs),2.63(1H,s),2.73(2H, brs),4.20(2H,brs),4.22(1H,s) 4.60(2H,s),6.88-7.35(13H,m)

Table 3

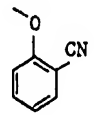
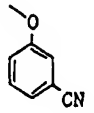
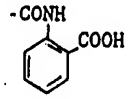
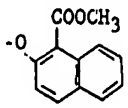
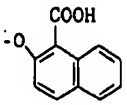
Ex.	R^1	B	m	p	A	Melting point(°C)	MS(M^+)	IR(cm^{-1}), NMR(ppm)
13	Cl	Ph	2	1		Decomposition point 160 (Oxalate)	431	IR(nujol):2220 NMR(DMSO-d_6):(Oxalate)2.52 (4H,m),3.25(4H,m),3.41(2H,t), 4.46(2H,t),4.49(1H,s), 7.13-7.75(13H,m)
14	Cl	Ph	2	1		168-170	431	IR(nujol):2220,1680 NMR(DMSO-d_6):(fumarate)2.51 (4H,brs),3.30(4H,brs),3.54 (2H,t),4.39(2H,t),4.55(1H,s), 6.15(4H,s),7.24-7.53(13H,m)
15	H	Ph	2	1		Decomposition point 223	443	IR(nujol):3580,3450,1670 NMR(DMSO-d_6):2.70-3.10(6H,m), 2.40-2.50(12H,m),3.14(2H,t) 4.36(1H,s),7.01-7.43(12H,m), 7.95-7.98(1H,m),8.45-8.48(1H,m)
16	Cl	Ph	2	1		Decomposition point 177-180 (Dihydrochloride)	514	IR(nujol):3400,1720,1600 NMR($CDCl_3$):3.54(4H,brs),3.83 (4H,brs),4.03(3H,s),4.43 (2H,brs),4.72(2H,brs),4.95 (1H,s),7.28-7.93(15H,m)
17	Cl	Ph	2	1		130-131	500	IR(nujol):3200,1580,1410 NMR($CDCl_3$):2.42(4H,brs), 2.53(4H,brs),2.68(2H,t), 4.22(1H,s),4.51(2H,t) 7.10-8.35(15H,m)

Table 4

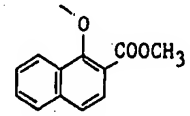
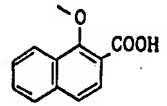
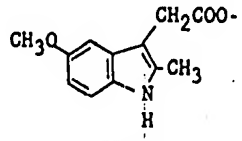
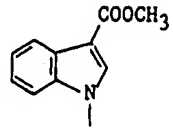
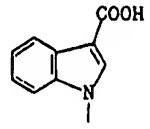
Ex.	R^1	B	m	p	A	Melting point(°C)	MS(M^+)	IR(cm^{-1}), NMR(ppm)
18	Cl	Ph	2	1		Decomposition point 197-200 (Dihydrochloride)	514	IR(nujol):3500,1710,1600 NMR($CDCl_3$):3.75(2H,t),3.96 (3H,s),4.12(4H,brd),4.53 (4H,brd), 4.63(2H,t),5.05 (1H,s),7.36-8.33(15H,m)
19	Cl	Ph	2	1		192-194 (Dihydrochloride)	500	IR(nujol):3450,1690,1600 NMR(DMSO-d_6):(2HCl)3.03 (2H,brs),3.76(5H,brs), 4.45(6H,brt), 7.40-8.34(16H,m)
20	Cl	Ph	2	1		- (amorphous)	531	NMR(DMSO-d_6):2.18(4H,brs),2.29 (3H,s),2.35(4H,brs),2.51 (2H,t),3.59(2H,s),3.70(3H,s), 4.07(2H,t),4.21(1H,s),6.57-7.42(12H,m),10.65(1H,brs)
21	Cl	Ph	2	1		- (foam)	487	NMR(DMSO-d_6):2.25(4H,brs), 2.46(4H,brs),2.67(2H,t),3.81 (3H,s),4.24(1H,s),4.30(2H,t), 7.15-7.57(11H,m),7.54-7.57(1H, m),8.03-8.06(1H,m),8.12(1H,s)
22	Cl	Ph	2	1		Decomposition point 105-110	474	IR(nujol):3350,1680 NMR(DMSO-d_6):2.28(4H,brs), 2.70(2H,t),3.35(4H,brs), 4.28(1H,s),4.32(2H,t), 7.16-7.99(14H,m),8.03(1H,s)

Table 5

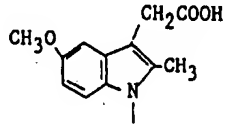
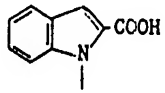
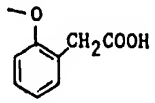
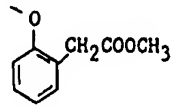
Ex.	R^1	B	m	p	A	Melting point(°C)	MS(M^+)	IR(cm^{-1}), NMR(ppm)
23	Cl	Ph	2	1		- (amorphous)	545	IR(nujol):1730 NMR(DMSO-d_6):2.25(4H,brs),2.31 (3H,s),2.44(4H,brs),2.50(2H,t), 3.54(3H,t),3.73(3H,s),4.12(2H, t),4.27(1H,s),6.66-7.44(12H,m)
24	Cl	Ph	2	1		Decomposition point 198	487 (Decarbo-xylated)	IR(nujol):3350,1700 NMR(DMSO-d_6):2.36(3H,s),2.50 (4H,brs),2.80(2H,brs),3.30 (4H,brs),3.60(2H,s),3.74(3H,s), 4.54(3H,brs); 6.72-7.45(12H,m), 11.36(1H,brs)
25	Cl	Ph	2	1		Decomposition point 171-177	429 (Decarbo-xylated)	IR(nujol):3400,1590 NMR(DMSO-d_6):2.28(4H,brs), 2.63(2H,t),3.60(5H,brs), 4.27(1H,s),4.68(2H,t), 7.09(1H,s),7.00-7.62(13H,m)
26	Cl	Ph	2	1		Decomposition point 184	464	IR(nujol):3400,1720,1600 NMR($CDCl_3$):2.51(4H,brs),2.76 (4H,brs),2.92(2H,t),3.56(2H,s), 4.11(2H,t),4.22(1H,s),5.45 (1H,brs),6.77-7.36(13H,m)
27	Cl	Ph	2	1		Decomposition point 168	478	IR(nujol):3400,1720,1590 NMR(DMSO-d_6):(2HCl)2.60(4H,brs), 2.98(4H,brs),3.35(2H,t),3.50 (3H,s),3.66(2H,s),4.38(2H,t), 4.82(1H,s),6.94-7.53(13H,m)

Table 6

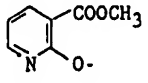
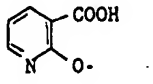
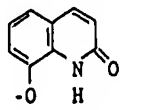
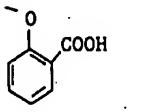
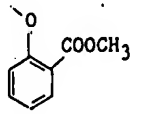
Ex.	R^1	B	m	p	A	Melting point(°C)	MS(M^+)	IR(cm^{-1}), NMR(ppm)
28	Cl	Ph	2	1		182-184	465	IR(nujol):3300,1720,1580 NMR(DMSO-d_6):(2HCl)2.87(4H,brs), 3.23(4H,brs),3.57(2H,t), 3.77(3H,s),4.67(1H,s), 4.73(2H,t),7.16-8.41(12H,m)
29	Cl	Ph	2	1		173-174	451	IR(nujol):3150,1700,1580 NMR(DMSO-d_6):(2HCl)2.85 (4H,brs),3.54(4H,brs),3.66 (2H,t),4.57(1H,s),4.70(2H,t), 7.13-8.37(12H,m),10.20(1H,brs)
30	H	Ph	2	1		Decomposition point 245-247	473	IR(nujol):3400,1670,1610 NMR(DMSO-d_6):(2HCl)3.22 (4H,brs),3.76(8H,brs), 4.49(1H,s),6.52-7.92 (14H,m),11.12(1H,s)
31	Cl	Py	2	1		- (amorphous)	451	IR(nujol):3350,1690 NMR(DMSO-d_6):2.35(4H,brs), 2.62(4H,brs),2.75(2H,t), 4.23(2H,t),4.45(1H,s),6.97-7.78(11H,m),8.44-8.46(1H,m)
32	Cl	Ph	2	2		Decomposition point 157 (Dihydrochloride)	478	IR(nujol):3400,1720 NMR(DMSO-d_6):(2HCl)2.09(4H,m), 3.19(6H,m),3.57(1H,s), 3.61(2H,t),3.69(3H,s), 4.47(2H,t),7.10-7.74(13H,m)

Table 7

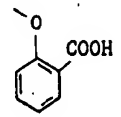
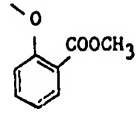
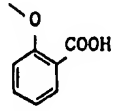
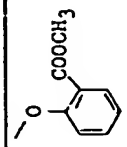
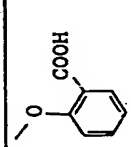
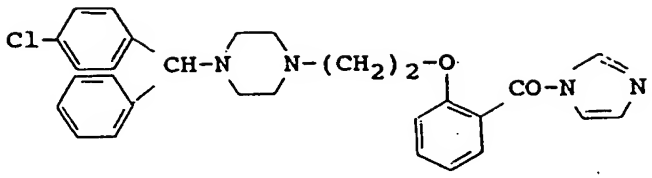
Ex.	R^1	B	m	p	A	Melting point(°C)	MS(M^+)	IR(cm^{-1}), NMR(ppm)
33	Cl	Ph	2	2		Decomposition point 164 (Dihydrochloride)	464	IR(nujol):3350,1700 NMR(DMSO-d_6):(2HCl)2.09 (4H,m),3.29(6H,m), 3.57(1H,s),3.60(2H,t), 4.47(2H,t),7.05-7.73(14H,m)
34	H	Py	2	1		- (oil)	431	IR(nujol):1725
35	H	Py	2	1		- (powder)	417	IR(nujol):3350,1708 NMR(DMSO-d_6):2.36(4H,brs), 2.63(4H,brs),2.76(2H,t),4.23 (2H,t),4.40(1H,s),6.97-7.77 (12H,m),8.30-8.44(1H,m)
36	Cl	Ph	3	1	-$COOCH_2CH_3$	- (Oil)	400	IR(neat):1730 NMR(DMSO-d_6):1.16(3H,t),1.61-1.69(2H,m),2.08-2.50(10H,m), 3.31(2H,brs),4.01(2H,q), 4.29(1H,s),7.15-7.43(9H,m)
37	Cl	Ph	3	1	-COOH	Decomposition point 183-185	372	IR(neat):3400,1710 NMR(DMSO-d_6):1.57-1.68(2H,m), 2.21(2H,t),2.30-2.43(8H,m), 2.40(2H,brs),4.30(1H,s) 7.15-7.44(9H,m)

Table 8

Ex.	R^1	B	m	p	A	Melting point(°C)	MS(M^+)	IR(cm^{-1}), NMR(ppm)
38	H	Ph	2	2		63-64	444	IR(nujol):3100,1705,1601 NMR($CDCl_3$):1.74-1.80(2H,m), 2.65(4H,dt),2.82(2H,t), 2.92(2H,t),3.30(2H,t), 3.82(3H,s),4.14(2H,t) 4.59(1H,s),6.94-7.79(14H,m)
39	H	Ph	2	2		- (foam) (Dihydrochloride)	429	IR(neat):3005,1713,1558 NMR($CDCl_3$):1.89-1.93(2H,m), 2.65(2H,t),2.76(2H,t), 2.94(2H,t),3.07(4H,dt), 4.37(2H,t),4.57(1H,s), 5.33(1H,brs),6.99-7.92(14H,m)

Example 40

2-[2-[4-[(4-Chlorophenyl)phenylmethyl]-1-piperazinyl]ethoxy]benzoylimidazole



In dimethylformamide, 1.5 g (3.3 mmol) of 2-[2-[4-[(4-chlorophenyl)phenylmethyl]-1-piperazinyl]ethoxy]-benzoic acid, which had been obtained in Example 4, were dissolved. Under ice cooling, 1.35 g (8.3 mmol) of carbodiimidazole were added to the resulting solution, followed by stirring at 80 °C for 20 minutes. After the reaction mixture was allowed to cool down, water was added and the resulting mixture was then extracted with ethyl ether. The ethyl ether layer was dried over anhydrous magnesium sulfate. The solvent was thereafter distilled off under reduced pressure. The residue so obtained was purified by chromatography on a column (chloroform), whereby the title compound was obtained. Melting point: powder (oxalate)

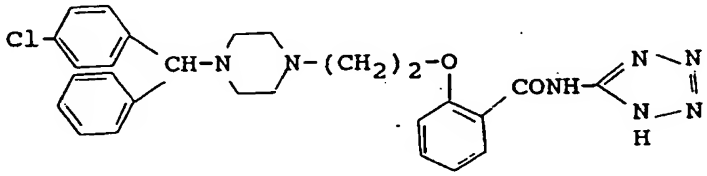
MS (m/z): 500(M^+)

IR (nujol) cm^{-1}: 1705

NMR (DMSO-d_6) δ: (oxalate) 2.38(2H,brs), 2.85(2H,brs), 3.12(2H,brs), 3.31(2H,brs), 3.40(2H,t), 4.34-(2H,m), 4.48(1H,s), 6.95-7.68(13H,m), 7.97(1H,s), 8.80(1H,s)

Example 41

2-[2-[4-[(4-Chlorophenyl)phenylmethyl]-1-piperazinyl]ethoxy]-N-1H-tetrazol-5-yl-benzamide



In dimethylformamide, 1.5 g (3.3 mmol) of the 2-[2-[4-[(4-chlorophenyl)phenylmethyl]-1-piperazinyl]-ethoxy]benzoic acid, which had been obtained in Example 4, were dissolved. Under ice cooling, 1.35 g (8.3 mmol) of carbodiimidazole were added to the resulting solution, followed by stirring at 80 °C for 20 minutes. The reaction mixture was allowed to cool down to room temperature. To the reaction mixture, 446 mg (4.3 mmol) of 5-amino-1H-tetrazole·H_2O were added, followed by stirring at 100 °C for one hour. The reaction mixture was poured into ice water to precipitate crystals. The crystals thus precipitated were collected by filtration and then purified by thin-layer chromatography, whereby 700 mg of the title compound were obtained. Yield: 39%.

(Sodium salt)

Melting point (decomposition point): 178 °C

Elemental analysis (1.2·H_2O)			
	C	H	N
Calculated:	57.74	5.28	17.45
Found:	57.90	5.14	17.10

IR (nujol) cm^{-1}: 3300, 1660

NMR (DMSO-d_6) δ: 2.06(4H,brs), 2.44(4H,brs), 2.74(2H,t), 4.05(1H,s), 4.29(2H,t), 7.05-7.93(14H,m)

(Hydrochloride)

Melting point (decomposition point): 197-200 °C

MS (m/z): 517(M^+)
IR (nujol) cm^{-1}: 3400, 1680

Examples 42-59

In accordance with the procedures of Example 41, the compounds of Examples 42-59 shown in Tables 9-12 were obtained. The names of the compounds will be described below.

Example 42

3-[2-[4-[(4-Chlorophenyl)phenylmethyl]-1-piperazinyl]ethoxy]-N-1H-tetrazol-5-yl-benzamide

Example 43

[3-[4-(Diphenylmethyl)-1-piperazinyl]N-propionyl]-N-1H-tetrazol-5-yl-anthranilamide

Example 44

2-[[2-[4-[(4-Chlorophenyl)phenylmethyl]-1-piperazinyl]ethyl]thio]-N-1H-tetrazol-5-yl-benzamide

Example 45

2-[3-[4-[(4-Chlorophenyl)phenylmethyl]-1-piperazinyl]propoxy]-N-1H-tetrazol-5-yl-benzamide

Example 46

2-[3-[4-(Diphenylmethyl)-1-piperazinyl]propoxy]N-1H-tetrazol-5-yl-benzamide

Example 47

1-[2-[4-[(4-Chlorophenyl)phenylmethyl]-1-piperazinyl]ethoxy]-N-1H-tetrazol-5-yl-naphthoamide

Example 48

2-[2-[4-[(4-Chlorophenyl)phenylmethyl]-1-piperazinyl]ethoxy]-N-1H-tetrazol-5-yl-naphthoamide

Example 49

2-[4-[(4-Chlorophenyl)phenylmethyl]-1-piperazinyl]ethyl]-N-1H-tetrazol-5-yl-anthranilamide

Example 50

2-[2-[4-[(4-Chlorophenyl)phenylmethyl]-1-piperazinyl]ethoxy]-N-1H-tetrazol-5-yl-acetamide

Example 51

1-[2-[4-[(4-Chlorophenyl)phenylmethyl]-1-piperazinyl]ethyl]-N-1H-tetrazol-5-yl-3-indoleamide

Example 52

1-[2-[4-[(4-Chlorophenyl)phenylmethyl]-1-piperazinyl]ethyl]-N-1H-tetrazol-5-yl-2-indoleamide

Example 53

2-[2-[4-[(4-Chlorophenyl)phenylmethyl]-1-piperazinyl]ethoxy]-N-1H-tetrazol-5-yl-phenylacetamide

Example 54

2-[2-[4-[(4-Chlorophenyl)phenylmethyl]-1-piperazinyl]ethoxy]-N-1H-tetrazol-5-yl-nicotinamide

Example 55

2-[2-[4-[(2-Phenyl-pyridylmethyl]-1-piperazinyl]ethoxy]-N-1H-tetrazol-5-yl-benzoic acid amide

Example 56

2-[2-[4-(Diphenylmethyl)-1-piperazinyl]ethoxy]-N-1H-tetrazol-5-yl-benzamide

Example 57

2-[2-[4-[2-(4-Chlorophenyl)pyridylmethyl]-1-piperazinyl]ethoxy]-N-1H-tetrazol-5-yl-benzoic acid amide

Example 58

2-[4-[(4-Chlorophenyl)phenylmethyl]-1-homopiperazinyl]ethoxy]-N-1H-tetrazol-5-yl-benzamide

Example 59

2-[2-[4-(Diphenylmethyl)-1-homopiperazinyl]ethoxy]-N-1H-tetrazol-5-yl-benzamide

Table 9

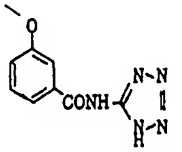
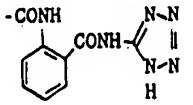
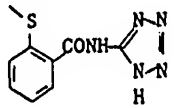
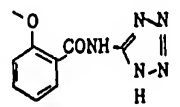
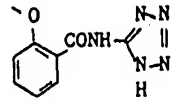
Ex.	R^1	B	m	p	A	Melting point(°C)	MS(M^+)	IR(cm^{-1}), NMR(ppm)
42	Cl	Ph	2	1		Decomposition point 178	518	IR(nujol):3175,1640 NMR(DMSO-d_6):2.32(4H,brs),2.56 (2H,brs),2.75(2H,t),3.45(2H, brs),4.14(2H,t),4.31(1H,s), 7.16-7.46(12H,m),7.63(2H,brs)
43	H	Ph	2	1		- (powder)		NMR(DMSO-d_6):2.22(2H,brs),2.35 (2H,brs),2.76(2H,t),3.18(2H, brs),4.23(2H,t),4.33(1H,t), 6.88(1H,s),7.16-7.44(14H,m), 7.61(1H,s),9.65(1H,s)
44	Cl	Ph	2	1		190-193 (Dihydrochloride)	533	IR(nujol):3200,1690 NMR(DMSO-d_6):(2HCl)2.89(4H,brs), 3.17(1H,s),3.26(2H,t),3.38(2H, t),3.90(4H,brs),4.84(1H,s), 7.27-7.76(13H,m),11.89(1H,s)
45	Cl	Ph	3	1		- (Powder)		IR(nujol):3350,1650 NMR(DMSO-d_6):1.96(2H,brs),2.29 (2H,brs),2.40-2.60(4H,m),3.48 (6H,brs),4.19(2H,t),4.29(1H,s), 7.07-7.52(12H,m),7.80(1H,brs)
46	H	Ph	3	1		194-199 (Dihydrochloride)	497	IR(nujol):2450,1680 NMR(DMSO-d_6):(2HCl)2.20(2H,t), 3.32(3H,brs),3.63(8H,brd), 4.21(2H,t),7.08-7.75(15H,m), 11.88(1H,s)

Table 10

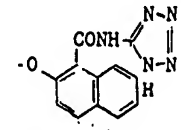
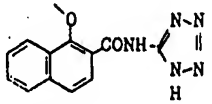
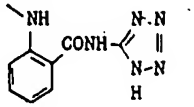
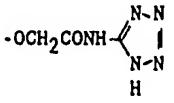
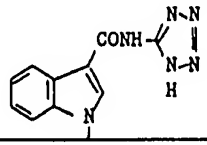
Ex.	R^1	B	m	p	A	Melting point(°C)	MS(M^+)	IR(cm^{-1}), NMR(ppm)
47	Cl	Ph	2	1			567	IR(nujol):3400,1670,1600 NMR(DMSO-d_6):2.25(4H,brs), 2.64(4H,brs),2.86(2H,t), 4.26(1H,s),4.36(12H,t), 7.18-8.09(17H,m)
48	Cl	Ph	2	1		Decomposition point 196-197 (Dihydrochloride)	567	IR(nujol):2400,1680,1580 NMR(DMSO-d_6):(2HCl)2.83(4H,brs), 3.61(2H,t),3,80(4H,brs), 4.43(2H,t),4.65(1H,s),7.35- 8.19(16H,m),12.51(1H,brs)
49	Cl	Ph	2	1		Decomposition point 171	516	NMR(DMSO-d_6):2.33(4H,brs), 2.89(4H,brs),3.27(2H,t),3.88 (2H,t),4.27(1H,s),6.59-6.78(2H,m), 6.96(1H,s),7.18-7.50(10H,m), 7.83-7.86(1H,m),10.79(1H,s)
50	Cl	Ph	2	1		Decomposition point 168 (Dihydrochloride)	455	IR(nujol):3400,3170,1700 NMR(DMSO-d_6):(2HCl)2.09(2Hs), 3.10(4H,brs),3.46(2H,t),3.65 (4H,brs),3.94(2H,brs),4.30(2H,s), 7.34-7.48(5H,m),7.76(7H,brs)
51	Cl	Ph	2	1		Decomposition point 162	540	IR(nujol):3200,1670 NMR(DMSO-d_6):2.27(4H,brs), 2.73(2H,t),3.50(4H,brs),4.28 (1H,s),4.35-4.47(2H,m), 7.15-8.56(15H,m),11.88(1H,s)

Table 11

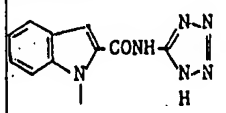
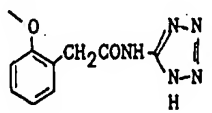
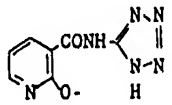
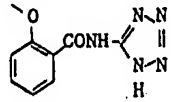
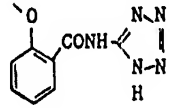
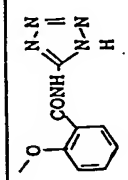
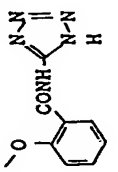
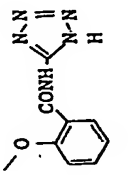
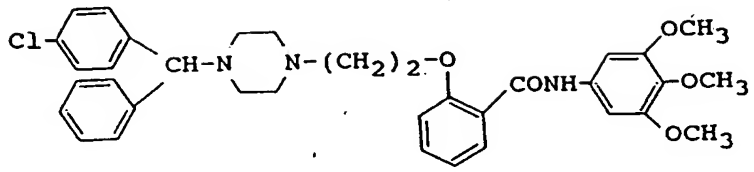
Ex.	R^1	B	m	p	A	Melting point(°C)	MS(M^+)	IR(cm^{-1}), NMR(ppm)
52	Cl	Ph	2	1		Decomposition point 163	540	IR(nujol):3400,3200,1650 NMR(DMSO-d_6):2.16(4H,brs), 2.41(4H,brs),2.56(2H,t), 4.07(1H,s),4.67(2H,t), 6.97-7.68(16H,m)
53	Cl	Ph	2	1		161	531	IR(nujol):3200,1670,1580 NMR(DMSO-d_6):2.24(4H,brs),2.67 (4H,brs),3.55(2H,t),3.70 (2H,s),4.03(2H,t),4.22(1H,s) 6.89-7.80(14H,m),11.88(1H,brs)
54	Cl	Ph	2	1		140-141	518	IR(nujol):3350,1670,1570 NMR(DMSO-d_6):2.25(4H,brs), 2.58(4H,brs),2.84(2H,t), 4.21(1H,s),4.56(2H,t) 7.17-8.40(14H,m)
55	H	Py	2	1		(powder)	484	IR(nujol):3250,3150 NMR(DMSO-d_6):2.16(4H,brs),2.78 (2H,t),3.51(4H,brs),4.22(1H,s) 4.31(2H,t),6.56(1H,s),7.07-7.92 (12H,m),8.39(1H,m),10.70(1H,brs)
56	H	Ph	2	1		Decomposition point 176	483	IR(nujol):3190,1660,1550 NMR(DMSO-d_6):2.24(4H,brs), 2.58(4H,brs),2.83(2H,t) 4.13(1H,s),4.33(2H,t), 7.12-8.25(16H,m)

Table 12

Ex.	R^1	B	m	p	A	Melting point(°C)	MS(M^+)	IR(cm^{-1}), NMR(ppm)
57	Cl	Py	2	1		(powder)	518	IR(nujol):3250,1640 NMR(DMSO-d_6):2.12(4H,brs),2.76(2H,t),3.42(4H,brs),4.23(1H,s),4.30(2H,t),6.55(1H,s),7.09-7.88(9H,m),8.40-8.42(1H,m),10.70(1H,brs)
58	Cl	Ph	2	2		(powder)	531	IR(nujol):3350,1670 NMR(DMSO-d_6):1.66(2H,brs),2.56(2H,t),3.00(4H,brs),3.10(4H,brs),4.35(2H,t),4.62(1H,s),6.97-7.72(15H,m)
59	H	Ph	2	2		99-100	497	NMR($CDCl_3$):1.78-1.93(2H,m),2.58(2H,t),2.64(2H,t),2.97(2H,t),3.02(2H,t),3.11(2H,t),4.35(2H,t),4.58(1H,s),5.96(1H,brs),6.67-8.08(14H,m),10.78(1H,brs)

Example 60

2-[2-[4-[(4-Chlorophenyl)phenylmethyl]-1-piperazinyl]ethoxy]-N-3,4,5-trimethoxyphenyl-benzamide



In 30 mℓ of ethyl acetate, 676 mg (3.67 mmol) of 3,4,5-trimethoxyaniline were dissolved. An aqueous solution (20 mℓ), in which were dissolved 2.0 g (3.69 mmol) of 2-[2-[4-[(4-chlorophenyl)phenylmethyl]-1-piperazinyl]ethoxy]benzoic acid chloride•dihydrochloride and 1.24 g of sodium hydrogencarbonate, was added to the resulting solution under ice cooling, followed by stirring for 30 minutes under ice cooling. The ethyl acetate layer was collected, washed successively with 10% sodium hydroxide and water and then, dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure. Crude crystals so obtained were recrystallized from a mixed solvent of chloroform and isopropyl ether, whereby 1.75 g of the title compound were obtained. Yield: 77%.

Melting point (decomposition point): 157-158 °C

MS (m/z): 615(M^+)

IR (nujol) cm^{-1}: 3320, 1655

NMR (DMSO-d_6) δ: 2.16(4H,brs), 2.50(4H,brs), 2.78(2H,t), 3.66(3H,s), 3.73(6H,s), 4.09(1H,s), 4.25(2H,t), 7.03(2H,s), 7.07-7.78(13H,m), 10.08(1H,s)

Examples 61-65

Following the procedures of Example 60, the compounds of Examples 61-65 shown in Table 13 were obtained. The followings are the names of the compounds:

Example 61

2-[2-[4-[(4-Chlorophenyl)phenylmethyl]-1-piperazinyl]ethoxy]-N-(3,5-dimethyl-4-hydroxyphenyl)benzamide

Example 62

2-[2-[4-[(4-Chlorophenyl)phenylmethyl]-1-piperazinyl]ethoxy]-thiazolidyl-2-yl-benzamide

Example 63

2-[2-[4-[(4-Chlorophenyl)phenylmethyl]-1-piperazinyl]ethoxy]-thiazol-2-yl-benzamide

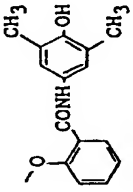
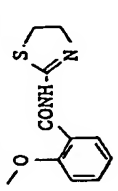
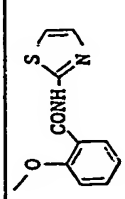
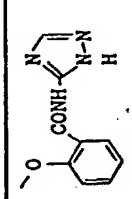
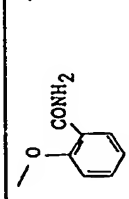
Example 64

2-[2-[4-[(4-Chlorophenyl)phenylmethyl]-1-piperazinyl]ethoxy]-N-1H-triazol-5-yl-benzamide

Example 65

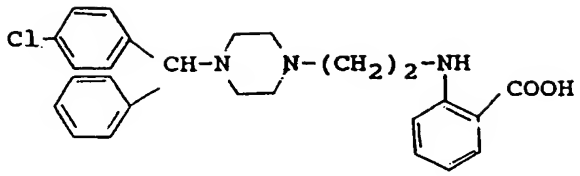
2-[2-[4-(4-Chlorophenyl)phenylmethyl]-1-piperazinyl]ethoxy]benzamide

Table 13

Ex.	R^1	B	m	p	A	Melting point(°C)	MS(M^+)	IR(cm^{-1}), NMR(ppm)
61	Cl	Ph	2	1		Decomposition point 198-200	569	NMR(DMSO-d_6):2.15(10H,brs), 2.50(4H,brs),2.77(2H,t), 4.03(1H,s),4.26(2H,t),7.05-7.51(14H,m),7.86-7.90(1H,m), 8.13(1H,brs),9.95(1H,s)
62	Cl	Ph	2	1		- (foam)	535	IR(nujol):3300,1670
63	Cl	Ph	2	1		136-138	533	IR(nujol):3250,1645 NMR(DMSO-d_6):2.24(4H,brs), 2.51(4H,brs),2.77(2H,t),4.18 (1H,s),4.33(2H,t),7.07-7.59 (14H,m),7.85-7.88(1H,m)
64	Cl	Ph	2	1		- (powder)	517	IR(nujol):3300,1660 NMR(DMSO-d_6):2.17(4H,m),2.50 (4H,m),2.75(2H,t),4.12(1H,s), 4.31(2H,t),7.08-7.40(13H,m),7.52 -7.59(1H,m),7.85-7.89(1H,m)
65	Cl	Ph	2	1		160-161	449	IR(nujol):3400,1660 NMR(DMSO-d_6):2.31(4H,brs), 2.49(4H,brs),2.71(2H,t), 4.20(2H,t),4.29(1H,s),6.99-7.88(13H,m),8.20(2H,brs)

Example 66

2-[[2-[4-[(4-Chlorophenyl)phenylmethyl]-1-piperazinyl]ethyl]amino]benzoic acid



In 1N sodium hydroxide, 800 mg (1.74 mmol) of the 1-[2-[4-[(4-chlorophenyl)phenylmethyl]-1-piperazyl]ethoxy]isatin,which had been obtained according to the procedures of Example 1, and 3 mℓ of tetrahydrofuran were dissolved, followed by the dropwise addition of 1 mℓ of a 30% aqueous hydrogen peroxide solution. After having been stirred at 70 °C for one hour, the reaction mixture was allowed to cool down and an aqueous solution of sodium sulfite was added. Further, acetic acid was added to the resulting mixture to adjust its pH to 3. Crystals so precipitated were purified by chromatography on a silica gel column (ethyl acetate), whereby 405 mg of the title compound were obtained. Yield: 52%.

Melting point: 205-206 °C

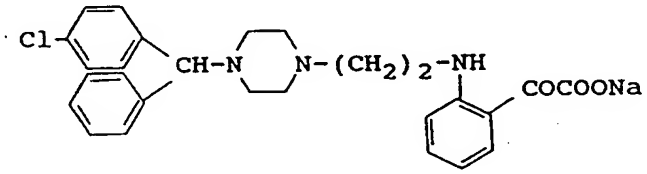
MS (m/z): 449(M^+)

IR (nujol) cm^{-1}: 3320, 1655

NMR (DMSO-d_6) δ: 2.32(4H,brs), 2.50(4H,brs), 2.58(2H,t), 3.21(2H,t), 4.27(1H,s), 6.52(1H,t), 6.79(1H,d), 7.18(1H,d), 7.26-7.46(11H,m), 7.76(1H,dd)

Example 67

Sodium 2-[[2-[4-[(4-chlorophenyl)phenylmethyl]-1-piperazinyl]ethyl]amino]-α-oxo-phenylacetate



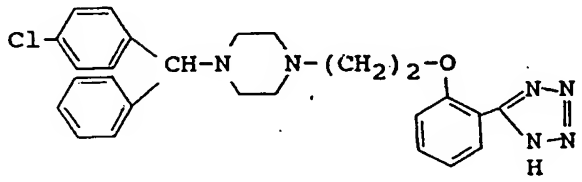
In 5 mℓ of tetrahydrofuran, 300 mg of 1-[2-[4-[(4-chlorophenyl)phenylmethyl]-1-piperazyl]ethoxy]isatin, which had been obtained in accordance with the procedures of Example 1, and 0.5 mℓ of a 1N aqueous sodium hydroxide solution were dissolved, followed by stirring at room temperature for 2 hours. The solvent was distilled off under reduced pressure. The residue was thereafter dissolved in water and purifed on polystyrene gel (HP-20), whereby the title compound was obtained.

Melting point (decomposition point): 130-133 °C (sodium-salt)

Elemental analysis:			
	C	H	N
Calculated:	64.86	5.44	8.40
Found:	64.83	5.70	8.17

Example 68

2-[2-[4-[(4-Chlorophenyl)phenylmethyl]-1-piperazinyl]ethoxy]-(N-1H-tetrazol-5-yl)-benzene



In 50 mℓ of toluene, 4.7 g (10.9 mmol) of the 2-[2-[4-[(4-chlorophenyl)phenylmethyl]-1-piperazinyl]-ethoxy]benzonitrile, which had been obtained in Example 13, and 10.9 g (32.7 mmol) of tri-n-butyltin azide were dissolved, followed by refluxing for two days. To the reaction mixture, 5.6 g of benzonitrile were added, followed by further refluxing until the excess tri-n-butyltin aside was eliminated. After the reaction mixture was allowed to cool down, the solvent was distilled off under reduced pressure. The residue so obtained was dissolved in a mixed solution of hydrochloric acid, dioxane and ethanol, followed by stirring for one hour. After the solvent was distilled off, a mixed solution of toluene and ethyl ether was added, whereby 4.34 g of the title compound were obtained as a precipitate. Yield: 72%.

Melting point: powder (dihydrochloride)

MS (m/z): 474(M^+)

IR (nujol) cm^{-1}: 3400

NMR (DMSO-d_6) δ: 2.41(2H,m), 2.65(7H,m), 2.86-2.92(2H,m), 4.19(2H,t), 4.32(2H,t), 6.92-7.54(14H,m), 8.31-8.34(1H,m)

Examples 69 & 70

Following the procedures of Example 68, the compounds of Examples 68 and 69 shown in Table 14 were obtained. The followings are the names of the compounds:

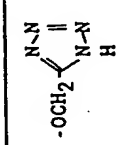
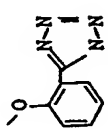
Example 69

2-[2-[4-[(4-Chlorophenyl)phenylmethyl]-1-piperazinyl]ethoxy]-1H-tetrazol-5-ylmethyl

Example 70

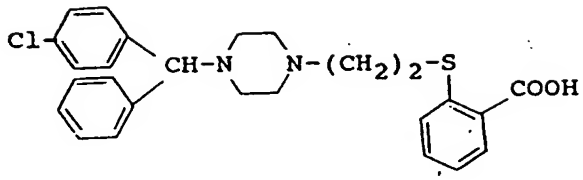
3-[2-[4-[(4-Chlorophenyl)phenylmethyl]-1-piperazinyl]ethoxy]-[N-1H-tetrazol-5-yl]-benzene

Table 14

Ex.	R^1	B	m	p	A	Melting point(°C)	MS(M^+)	IR(cm^{-1}), NMR(ppm)
69	Cl	Ph	2	1		Decomposition point 225 (Dihydrochloride)	412	IR(nujol):3450 NMR(DMSO-d_6):(2HCl)2.60-3.80(11H,m),3.95(2H,t),4.91(2H,s),7.38-7.48(5H,m),7.77(4H,brs)
70	Cl	Ph	2	1		220-222 (Dihydrochloride)	474	IR(nujol):3400 NMR(DMSO-d_6):(2HCl)3.14(4H,brs),3.20-4.50(9H,m),4.54(2H,brs),5.33(1H,brs),7.20-7.75(13H,m)

Example 71

2-[[2-[4-[(4-Chlorophenyl)phenylmethyl]-1-piperazinyl]ethyl]thio]benzoic acid



In a 15:85 mixed solution of water and tetrahydrofuran, 5.0 g (12 mmol) of 2-[4-[(4-chlorophenyl)-phenylmethyl]-1-piperazinyl]ethylchloride•dihydrochloride were dissolved, followed by the dropwise addition of 4.0 g (39 mmol) of triethylamine under an argon stream. To the resulting solution, 2.2 g (14 mmol) of thiosalicylic acid were added and they were stirred at 50°C for 8 hours. After the reaction mixture was allowed to cool down, the solvent was distilled off under reduced pressure. Water (200 mℓ) was added to the residue, followed by extraction with 200 mℓ of ethyl acetate. The ethyl acetate layer was dried over anhydrous magnesium sulfate and the solvent was distilled off. The residue so obtained was purified by chromatography on a silica gel column (chloroform: methanol = 10:1), whereby 2.8 g of the title compound were obtained in an oily form. Yield: 51%.

Melting point: 181-184°C (hydrochloride)

MS (m/z): 466(M^+)

IR (nujol) cm^{-1}: 2280, 1700, 1590

NMR (DMSO-d_6) δ: (dihydrochloride) 3.09(4H,brs), 3.35(4H,brs), 3.41(2H,t), 3.60(3H,t), 3.64(1H,s), 7.24-7.93(14H,m)

Examples 72-74

In accordance with the procedures of Example 71, the compounds of Examples 72-74 shown in Table 15 were obtained. The followings are the names of the compounds.

Example 72

Ethyl 2-[[2-[4-[(4-Chlorophenyl)phenylmethyl]-1-piperazinyl]ethyl]thio]acetate

Example 73

2-[[2-[4-[(4-Chlorophenyl)phenylmethyl]-1-piperazinyl]ethyl]thio]acetic acid

Example 74

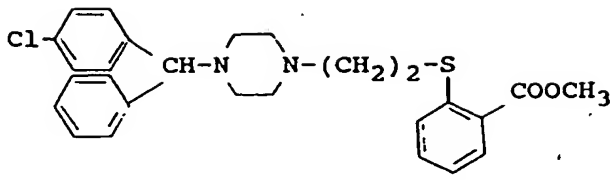
2-[[2-[4-[(4-Chlorophenyl)phenylmethyl]-1-piperazinyl]ethyl]thio]nicotinic acid

Table 15

Ex.	R^1	B	m	p	A	Melting point(°C)	MS(M^+)	IR(cm^{-1}), NMR(ppm)
72	Cl	Ph	2	1	-S-$CH_2COOCH_2CH_3$	(powder) (Oxalate)	432!	NMR(DMSO-d_6):(oxalate)1.21(3H, t),2.98-3.04(2H,m),3.26(4H, brs),3.37-3.42(2H,m),3.50 (2H,s),3.65(5H,brs),4.12(2H,q), 7.35-7.51(4H,m),7.87(5H,t)
73	Cl	Ph	2	1	-S-CH_2COOH	Decomposition point 170-172 (Oxalate)	404	IR(nujol):3450,1720 NMR(DMSO-d_6):(oxalate)2.50 (4H,m),2.86-2.91(2H,m),3.20-3.26(6H,m),3.36(2H,s),4.50 (1H,s),7.23-7.48(9H,m)
74	Cl	Ph	2	1		185 (Dihydrochloride)	467	IR(nujol):3400,1720,1560 NMR(DMSO-d_6):(2HCl)2.93 (4H,brs),3.39(4H,brs),3.60 (2H,t),4.62(3H,brs), 7.25-8.70(13H,m)

Example 75

Methyl 2-[2-[4-[(4-chlorophenyl)phenylmethyl]-1-piperazinyl]ethyl]thio]benzoate



In 20 ml of anhydrous dichloromethane, 1.1 g (2.36 mmol) of the 2-[[2-[4-[(4-chlorophenyl)-phenylmethyl]-1-piperazinyl]ethyl]thio]benzoic acid, which had been obtained in Example 71, were suspended, followed by the dropwise addition of 0.4 g (3.53 mmol) of thionyl chloride and stirring for 30 minutes, both under ice cooling. After the solvent was distilled off under reduced pressure, 20 ml of anhydrous methanol were added to the residue and the resulting mixture was stirred at room temperature for 30 minutes. The solvent was distilled off under reduced pressure. Water (50 ml) was added to the residue, followed by extraction with 50 ml of ethyl acetate. The ethyl acetate layer was washed with a saturated aqueous solution of sodium hydrogencarbonate and then dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure. The residue so obtained was purified by chromatography on a silica gel column (ethyl acetate:n-hexane = 2:1), whereby 0.94 g of the title compound was obtained in an oily form. Yield: 85%.

Melting point: 170-171 °C (hydrochloride)

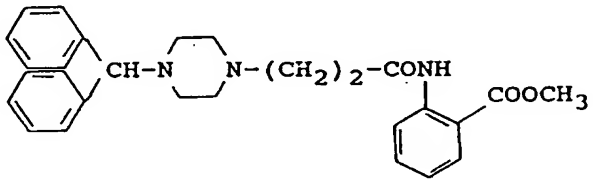
MS (m/z): 480(M^+)

IR (nujol) cm^{-1}: 2300, 1710, 1590

NMR (DMSO-d_6) δ: (dihydrochloride) 2.38(4H,brs), 2.80(4H,brs), 3.17(2H,t), 3.45(2H,t), 3.83(3H,s), 4.53-(1H,s), 7.20-7.92(13H,m)

Example 76

Methyl [3-[4-(diphenylmethyl)-1-piperazinyl]N-propionyl]anthranilate



In 100 ml of toluene, 5.92 g (23.5 mmol) of diphenylmethylpiperazine, 5.67 g (23.5 mmol) of methyl N-3-chloropropionylanthranilate and 6.23 g (43.9 mmol) of sodium carbonate were suspended, followed by refluxing for 12 hours. The reaction mixture was allowed to cool down and water was added to it, followed by extraction with ethyl acetate. The ethyl acetate layer was washed with water and then dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure. The residue so obtained was purified by chromatography on a silica gel column (n-hexane: ethyl acetate = 1:2), whereby 9.2 g of the title compound were obtained. Yield: 86%.

Melting point: 120-122 °C

MS (m/z): 457(M^+)

IR (nujol) cm^{-1}: 3280, 1710, 1690

NMR (DMSO-d_6) δ: 2.31(4H,brs), 2.48(4H,brs), 2.50(2H,t), 3.80(3H,s), 4.24(1H,s), 7.13-8.27(14H,m)

Preparation Example 1

Compound of Example 41	50 g
Lactose	315 g
Corn starch	125 g
Crystalline cellulose	25 g

The above ingredients were mixed uniformly, followed by the addition of 200 ml of a 7.5% aqueous solution of hydroxypropylcellulose. The resultant mixture was granulated through a screen of 0.5 mm in diameter by an extrusion granulator. Immediately after that, the resultant granules were rounded by a Marumerizer and then dried, whereby granules were obtained.

The dried granules so obtained were coated with 1.9 kg of a film coating solution of the below-described composition by using a fluidized-bed granulator, whereby enteric coated granules were obtained.

Composition of the coating solution:

Hydroxypropylmethylcellulose phthalate	5.0 wt.%
Stearic acid	0.25 wt.%
Methylene chloride	50.0 wt.%
Ethanol	44.75 wt.%

Preparation Example 2

Compound of Example 45	20 g
Lactose	100 g
Corn starch	36 g
Crystalline cellulose	30 g
Carboxymethylcelullose calcium	10 g
Magnesium stearate	4 g

The above ingredients were mixed uniformly and then, pressed into 200-mg tablets by a punch of 7.5 mm in diameter on a single punch tableting machine.

A coating solution of the below composition was sprayed to the tablets to apply 10 mg of a coating per tablet, whereby enteric film-coated tablets were obtained.

Composition of the coating solution:

Hydroxypropylmethylcellulose phthalate	8.0 wt.%
Glycerin fatty acid ester	0.4 wt.%
Methylene chloride	50.0 wt.%
White beeswax	0.1 wt.%
Isopropanol	41.5 wt.%

Preparation Example 3

Compound of Example 46	100 mg
Sodium acetate	2 mg
Acetic acid (for adjustment of pH to 5.8)	q.s.
Distilled water for injection	q.s.
	Total 10 mℓ/vial

An injection was obtained according to the above formulation in a manner known *per se* in the art.

Preparation Example 4

Compound of Example 69	0.1 wt.%
Ethanol	20.0 wt.%
Liquefied gas ("Propellant 114")	49.2 wt.%
Liquefied gas ("Propellant 12")	30.7 wt.%

An aerosol was prepared according to the above formulation in a manner known *per se* in the art.

Tests

Test 1 Antihistamic effects

From a Hartley male guinea pig (300-600 g in weight), the ileum was isolated. The ileum was attached to a holder under a vesting tension of 0.5 g in a Magnus bath (30 • C, under aeration) filled with 10 mℓ of the Tyrode solution. As a contraction reaction of the isolated ileum caused by histamine (3×10^{-7} mole), an isometrical change in muscular tension was measured. The ileum was treated with the test compound for 3 minutes before the addition of histamine to study its effects and then its antihistamic action (50% inhibition concentration: IC_{50} value) was determined.

As a result, each compound showed an IC_{50} value of from 0.14 to 1.59 μM. Incidentally, the IC_{50} value of Cetiridine (the compound disclosed in Japanese Patent Laid-Open No. 149282/1982) was determined as a control. Its IC value was 2.40 μM.

Test 2 Antiallergic effects

The back of a male SD rat (150-250 g in weight) was shaved in advance. Physiological saline and 0.1 mℓ of anti DNP-AS (Dinitrophenyl conjugated Ascaris) IgE serum which had been diluted to a suitable concentration with physiological saline were intradermally injected there. Fourty-eight hours after sensitization, the animals were challenged with 1 mℓ of 0.5% Evans blue physiological saline containing 2.5 mg/mℓ of DNP-BSA (dinitrophenyl conjugated bovine serum albumin) via the tail vein. Thirty minutes later, they were sacrificed under exsanguination and the dorsal skin was removed and the exuded dye was measured according to the method proposed by Harada et al. [Allergy, 15, 1-7(1966)]. The leaked color amount caused by the passive cutaneous anaphylaxis (PCA) was determined by subtracting the leaked color amount of the site to which physiological saline was administered from that of the PCA site. Each test compound was suspended in 5% gum arabic or 0.5% methylcellulose and the resulting suspension was orally administered at the rate of 10 mg/4 mℓ/kg one hour before the administration of antigen. The efficacy of the test compound was evaluated by an ihibition rate (antiallergic effects) of the leaked color amount. The results are shown in Table 16.

Table 16

Test compound	Antiallergic effects (%)
Compound of Example 5 (1/2 fumarate)	86.4
Compound of Example 9	61.9
Compound of Example 41 (Sodium salt)	52.3
Compound of Example 44	54.7
Compound of Example 45	72.4
Compound of Example 46	59.8
Compound of Example 50	60.4
Compound of Example 69	81.0

Test 3 Toxicity Test

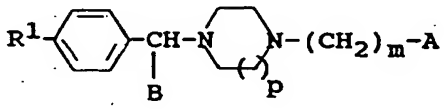
Ten 4-5 week old ICR mice (Charles River Co., Ltd.) were employed in groups, each consisting of 10 mice. The compounds of the Examples were separately suspended in 5% gum arabic. The suspension were each orally administered at a dose of 1000 mg/kg and the mice were observed for 7 days. As a result, no case of death caused by the toxicity of any of the invention compounds was observed.

Industrial Applicability

The compound according to the present invention have strong antihistamic and antiallergic effects and have a high degree of safety so that they are useful as therapeutic agents for various allergic diseases, for example, as anti-inflammatory agents, therapeutics for nephritis, hepatitis or pancreatitis, preventives and/or therapeutics for respiratory diseases, and antiasthmatic drugs.

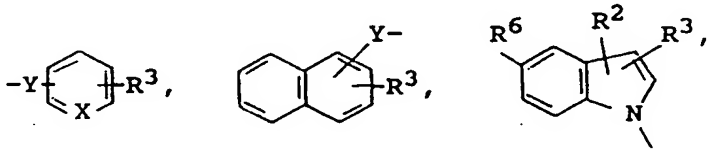
Claims

1. A piperazine derivative represented by the following formula (I):



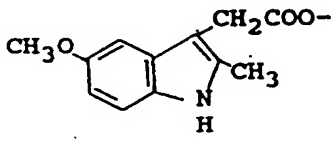
(I)

wherein B represents a phenyl or pyridinyl group, m stands for an integer of 2 or 3, p stands for an integer of 1 or 2, R^1 represents a hydrogen or halogen atom, A represents $-COOR^2$, $-Y-(CH_2)_n-R^3$,

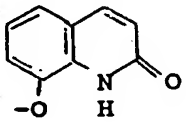


in which R^2 represents a hydrogen atom or a lower alkyl group, Y represents a sulfur or oxygen atom, NH or ←CONH- (← indicates a bond with a $(CH_2)_m$ group), n stands for an integer of 0 to 3, R^3 represents a cyano, amino, hydroxymethyl, 1H-tetrazole, 1-imidazolylcarbonyl, $-CO-COOR^4$, $-(CH_2)_t-COOR^4$ or $-(CH_2)_t-CONH-R^5$ group (R^4: hydrogen atom or lower alkyl group; t: integer of 0 to 3; and

R^5: 1H-tetrazole, thiazol-2-yl, thiazolin-2-yl, triazol-5-yl, trimethoxyphenyl or 3,5-dimethyl-4-hydroxyphenyl group), X represents CH or a nitrogen atom and R^6 represents a hydrogen atom or a lower alkoxyl group,



or



with the proviso that either case where R^1, B, p, m and A represent a hydrogen atom, a phenyl group, 1, 2 and -NH-C_6H_4-$COOR^4$, respectively, or where R^1, B, p, m and A represent a chlorine atom, a phenyl group, 1, 2 and -O-CH_2COOH, respectively is excluded; or a salt thereof.

2. An antihistamic agent comprising as an active ingredient the piperazine derivative according to claim 1.

3. An antiallergic agent comprising as an active ingredient the piperazine derivative according to claim 1.

4. An antiallergic agent according to claim 3, which is an antiasthmatic drug.

INTERNATIONAL SEARCH REPORT

International Application No PCT/JP92/00833

I. CLASSIFICATION OF SUBJECT MATTER (If several classification symbols apply, indicate all) [6]

According to International Patent Classification (IPC) or to both National Classification and IPC Int. Cl[5]

C07D295/08, C07D295/10, C07D295/12, C07D295/14, C07D213/36, C07D213/80, C07D215/26, C07D401/12, C07D403/12, C07D257/04, C07D249/10, C07D209/14

II. FIELDS SEARCHED

Minimum Documentation Searched [7]

Classification System	Classification Symbols
IPC	C07D295/08, C07D295/10, C07D295/12, C07D295/14, C07D213/36, C07D213/80, C07D215/26, C07D401/12, C07D403/12, C07D257/04, C07D249/10, C07D209/14

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched [8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT [9]

Category [10]	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No. [13]
P	JP, A, 3-246287 (Hokuriku Seiyaku K.K.), November 1, 1991 (01. 11. 91), (Family: none)	1-4

[10] Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
September 11, 1992 (11. 09. 92)	October 6, 1992 (06. 10. 92)
International Searching Authority	**Signature of Authorized Officer**
Japanese Patent Office	